COX-2-derived prostanoids and oxidative stress additionally reduce endothelium-mediated relaxation in old type 2 diabetic rats

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Résumé en anglais	Endothelial dysfunction in resistance arteries alters end organ perfusion in type 2 diabetes. Superoxides and cyclooxygenase-2 (COX-2) derivatives have been shown separately to alter endothelium-mediated relaxation in aging and diabetes but their role in the alteration of vascular tone in old diabetic subjects is not clear, especially in resistance arteries. Consequently, we investigated the role of superoxide and COX-2-derivatives on endothelium-dependent relaxation in 3 and 12 month-old Zucker diabetic fatty (ZDF) and lean (LZ) rats. Mesenteric resistance arteries were isolated and vascular tone was investigated using wire-myography. Endothelium (acetylcholine)-dependent relaxation was lower in ZDF than in LZ rats (60 versus 84% maximal relaxation in young rats and 41 versus 69% in old rats). Blocking NO production with L-NAME was less efficient in old than in young rats. L-NAME had no effect in old ZDF rats although eNOS expression level in old ZDF rats was similar to that in old LZ rats. Superoxide level and NADPH-oxidase subunits (p67phox and gp91phox) expression level were greater in ZDF than in LZ rats and were further increased by aging in ZDF rats. In young ZDF rats reducing superoxide level with tempol restored acetylcholine-dependent relaxation to the level of LZ rats. In old ZDF rats tempol improved acetylcholine-dependent relaxation without increasing it to the level of LZ rats. COX-2 (immunolabelling and Western-blot) was present in arteries of ZDF rats and absent in LZ rats. In old ZDF rats arterial COX-2 level was higher than in young ZDF rats. COX-2 blockade with NS398 restored in part acetylcholine-dependent relaxation in arteries of old ZDF rats and the combination of tempol and NS398 fully restored relaxation in control (LZ rats) level. Accordingly, superoxide production and COX-2 derivatives together reduced endothelium-dependent relaxation in old ZDF rats whereas superoxides alone attenuated relaxation in young ZDF or old LZ rats.
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